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ACVM GUIDELINE FOR GOOD MANUFACTURING PRACTICE

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Endorsement:
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INTRODUCTION

Guidelines for Good Manufacturing Practice (GMP) for agricultural compounds and veterinary medicines are an important element in achieving acceptable standards for the manufacture and handling of such products. These guidelines are an internationally accepted set of guidelines that describe proven systems and procedures for the production of quality products. They also contain the documentation requirements to provide a traceable history of the production and distribution of every batch of product.

Permission was sought and received to adopt the 1992 Pharmaceutical Inspection Convention (PIC) Guide to GMP as the guidelines for manufacturing standards in New Zealand. The Pharmaceutical Inspection Convention is a multinational agreement among government authorities to exchange information on the state of GMP compliance by manufacturers. It provides a basis for mutual recognition of inspection standards between various countries and lays emphasis on quality management to achieve safety and efficacy of products. With a few minor adaptations, this code has been adopted to cover the manufacture of agricultural compounds and veterinary medicines in New Zealand.

The guidelines are presented in sections, each addressing a specific topic. In addition to the general matters of GMP outlined in the nine sections of this code, a series of annexes providing details about specific areas of activity is included. For some manufacturing processes, different annexes will apply simultaneously. For example, the annexes on sterile preparations and on manufacture of immunological veterinary medicinal products should be consulted for the preparation of vaccines.

A glossary of some terms used in the code has been incorporated after the annexes.

It is recognised that there are acceptable methods, other than those described in these guidelines, that are capable of achieving the principles of this code. This code is not intended to place any restraint upon the development of new concepts or new technologies that have been validated and provide a level of Quality Assurance at least equivalent to that set out in this code.

1 QUALITY MANAGEMENT

Principle

The holder of a manufacturing authorisation must manufacture veterinary medicinal products* so as to ensure that they are fit for their intended use, comply with the requirements of the manufacturing authorisation and do not place animals at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by the distributors. To achieve the quality objective reliably, there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice and thus Quality Control. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance system should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities.

1.1 The basic concepts of Quality Assurance, Good Manufacturing Practice and Quality Control are interrelated. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of medicinal products.

* generally referred to throughout as 'product(s)'

Quality Assurance

1.2 Quality Assurance is a wide ranging concept that covers all matters that individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the object of ensuring that products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this guide.

The system of Quality Assurance appropriate for the manufacture of products should ensure that:

a) products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice (and Good Laboratory Practice);
b) production and control operations are clearly specified and Good Manufacturing Practice adopted;
c) managerial responsibilities are clearly specified;
d) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
e) all necessary controls on intermediate products, and any other in-process controls and validations are carried out;
f) the finished product is correctly processed and checked, according to the defined procedures;

g) products are not sold or supplied before an authorised person has documented that each production batch has been produced and controlled in accordance with the specifications of the manufacturing authorisation and any other relevant regulations;
h) satisfactory arrangements exist to ensure, as far as possible, that the products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf-life;
i) there is a procedure for self inspection and/or quality audit that regularly appraises the effectiveness and applicability of the Quality Assurance system.

Good Manufacturing Practice for Veterinary Medicinal Products

1.3 Good Manufacturing Practice (GMP) is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the manufacturing authorisation.

Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;
b) critical steps of manufacturing processes and significant changes to the process are validated;
c) all necessary facilities for GMP are provided including:
   - appropriately qualified and trained personnel;
   - adequate premises and space;
   - suitable equipment and services;
   - correct materials, containers and labels;
   - approved procedures and instructions;
   - suitable storage and transport;
d) instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
e) operators are trained to carry out procedures correctly;
f) records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;
g) records of manufacture including distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
h) the distribution (wholesaling) of the products minimises any risk to their quality;
i) a system is available to recall any batch of product from sale or supply;
j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

Quality Control

1.4 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of Quality Control are that:

a) adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;
c) test methods are validated;
d) records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;
e) the finished products contain active ingredients complying with the qualitative and quantitative composition of the manufacturing authorisation, are of the purity required, and are enclosed within their proper container and correctly labelled;
f) records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
g) no batch of product is released for sale or supply prior to documented approval by an authorised person that it is in accordance with the product specifications;
h) sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

2 PERSONNEL

Principle

The establishment and maintenance of a satisfactory system of Quality Assurance and the correct manufacture of veterinary medicinal products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks that are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them, and receive initial and continuing training, including hygiene instructions, relevant to their needs.

General

2.1 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

2.2 The manufacturer must have an organisation chart. People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.

Key personnel

2.3 Key personnel include the head of Production, the head of Quality Control and, if at least one of these persons is not responsible for the release of products, the authorised person(s) designated for the purpose. Normally key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organisations, it may be necessary to delegate some of the functions listed in 2.5, 2.6 and 2.7.

2.4 Not applicable in New Zealand.

2.5 The head of the Production Department generally has the following responsibilities:

a) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
b) to approve the instructions relating to production operations and to ensure their strict implementation;
c) to ensure that the production records are evaluated and signed by an authorised person before they are sent to the Quality Control Department;
d) to check the maintenance of the department, premises and equipment;

e) to ensure that the appropriate validations are done;
f) to ensure that the required initial and continuing training of department personnel is carried out and adapted according to need.

2.6 The head of the Quality Control Department generally has the following responsibilities:

a) to approve or reject, as appropriate, starting materials, packaging materials, and intermediate, bulk and finished products;
b) to evaluate batch records;
c) to ensure that all necessary testing is carried out;
d) to approve specifications, sampling instructions, test methods and other Quality Control procedures;
e) to approve and monitor any contract analysts;
f) to check the maintenance of the department, premises and equipment;
g) to ensure that the appropriate validations are done;
h) to ensure that the required initial and continuing training of department personnel is carried out and adapted according to need.

Other duties of the Quality Control Department are summarised in Section 6.

2.7 The heads of Production and Quality Control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include:

- the authorisation of written procedures and other documents, including amendments;
- the monitoring and control of the manufacturing environment;
- plant hygiene;
- process validation;
- training;
- the approval and monitoring of suppliers of materials;
- the approval and monitoring of contract manufacturers;
- the designation and monitoring of storage conditions for materials and products;
- the retention of records;
- the monitoring of compliance with the requirements of GMP;
- the inspection, investigation, and taking of samples, in order to monitor factors that may affect product quality.

Training

2.8 The manufacturer should provide training for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.9 Besides the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.

2.10 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, should be given specific training.

2.11 Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

2.12 The concept of Quality Assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

Personal hygiene

2.13 Detailed hygiene programmes should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take them into the production and control areas. Hygiene programmes should be promoted by management and widely discussed during training sessions.

2.14 All personnel should receive a medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.

2.15 Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.

2.16 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

2.17 Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected should be forbidden.

2.18 Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.

2.19 Personnel should be instructed to use the hand washing facilities.

2.20 Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in the annexes.

3 PREMISES AND EQUIPMENT

Principle

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products.

Premises

General

3.1 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.2 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3.3 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

3.4 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.5 Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

Production areas

3.6 In order to minimise the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitising materials (e.g. penicillins: see also Annex 4.7) or biological preparations (e.g. from live micro-organisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

3.7 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.8 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

3.9 Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

3.10 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

3.11 Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

3.12 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.

3.14 In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross-contamination and facilitate cleaning.

3.15 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

3.16 Production areas should be well lit, particularly where visual on-line controls are carried out.

3.17 In-process controls may be carried out within the production area provided they do not carry any risk for the production.

Storage areas

3.18 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials; intermediate, bulk and finished products; products in quarantine, released, rejected, returned or recalled.

3.19 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity), these should be provided, checked and monitored.

3.20 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

3.21 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.

3.22 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

3.23 Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

3.24 Highly active materials or products should be stored in safe and secure areas.

3.25 Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

Quality control areas

3.26 Normally, quality control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals and radioisotopes, which should also be separated from each other.

3.27 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

3.28 Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

3.29 Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

Ancillary areas

3.30 Rest and refreshment rooms should be separate from other areas.

3.31 Facilities for changing clothes, and for washing and toilet purposes, should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.

3.32 Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

3.33 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

Equipment

3.34 Manufacturing equipment should be designed, located and maintained to suit its intended purpose.

3.35 Repair and maintenance operations should not present any hazard to the quality of the products.

3.36 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures, and stored only in a clean and dry condition.

3.37 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.

3.38 Equipment should be installed in such a way as to prevent any risk of error or of contamination.

3.39 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

3.40 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

3.41 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

3.42 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

3.43 Distilled, deionised and, where appropriate, other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

3.44 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

4 DOCUMENTATION

Principle

Good documentation constitutes an essential part of the Quality Assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications, manufacturing formulae and instructions, procedures, and records must be free from errors and available in writing. The legibility of documents is of paramount importance.

General

4.1 *Specifications* describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Manufacturing formulae, processing and packaging instructions state all the starting materials used and lay down all processing and packaging operations.

Procedures give directions for performing certain operations, e.g. cleaning, clothing, environmental control, sampling, testing, equipment operations.

Records provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product.

4.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing authorisation.

4.3 Documents should be approved, signed and dated by appropriate and authorised persons.

4.4 Documents should have unambiguous contents; title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

4.5 Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.

4.6 Documents should not be handwritten, although, where documents require the entry of data, these entries may be made in clear, legible, indelible handwriting. Sufficient space should be provided for such entries.

4.7 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

4.8 The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of products are traceable. They should be retained for at least one year after the expiry date of the finished product.

4.9 Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorised persons should be able to enter or modify data in the computer and there should be a record of changes and deletions; access should be restricted by passwords or other means and the result of entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that the data are readily available throughout the period of retention.

Documents required

Specifications

4.10 There should be appropriately authorised and dated specifications for starting and packaging materials, and finished products; where appropriate, they should also be available for intermediate or bulk products.

Specifications for starting and packaging materials

4.11 Specifications for starting and primary or printed packaging materials should include, if applicable:

a) a description of the materials, including:
   - the designated name and the internal code reference;
   - the reference, if any, to a pharmacopoeial monograph;
   - the approved suppliers and, if possible, the original producer of the products;
   - a specimen of printed materials;

b) directions for sampling and testing or reference to procedures;
c) qualitative and quantitative requirements with acceptance limits;
d) storage conditions and precautions;
e) the maximum period of storage before re-examination.

Specifications for intermediate and bulk products

4.12 Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used for the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

4.13 Specifications for finished products should include:

a) the designated name of the product and the code reference where applicable;
b) the formula or a reference to it;
c) a description of the pharmaceutical form and package details;
d) directions for sampling and testing or a reference to procedures;
e) the qualitative and quantitative requirements, with the acceptance limits;
f) the storage conditions and any special handling precautions, where applicable;
g) the shelf-life.

Manufacturing formula and processing instructions

Formally authorised manufacturing formula and processing instructions should exist for each product and batch size to be manufactured. They are often combined in one document.

4.14 The manufacturing formula should include:

a) the name of the product, with a product reference code relating to its specification;
b) a description of the pharmaceutical form, strength of the product and batch size;
c) a list of all starting materials to be used, with the amount of each, described using the designated name and a reference that is unique to that material; mention should be made of any substance that may disappear in the course of processing;
d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

4.15 The processing instructions should include:

a) a statement of the processing location and the principal equipment to be used;
b) the methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);
c) detailed stepwise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);
d) the instructions for any in-process controls with their limits;
e) where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable;
f) any special precautions to be observed.

Packaging instructions

4.16 There should be formally authorised packaging instructions for each product, pack size and type. These should normally include, or have a reference to, the following:

a) name of the product;
b) description of its pharmaceutical form, and strength where applicable;
c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
e) where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf-life of the product;
f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
h) details of in-process controls with instructions for sampling and acceptance limits.

Batch processing records

4.17 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved manufacturing formula and processing instructions. The method of preparation of such records should be designed to avoid transcription errors. The record should carry the number of the batch being manufactured.

Before any processing begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use.

During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations:

a) the name of the product;
b) dates and times of commencement, of significant intermediate stages and of completion of production;
c) name of the person responsible for each stage of production;
d) initials of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);
e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
f) any relevant processing operation or event and major equipment used;

g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
h) the product yield obtained at different and pertinent stages of manufacture;
i) notes on special problems including details, with signed authorisation for any deviation from the manufacturing formula and processing instructions.

Batch packaging records

4.18 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the packaging instructions and the method of preparation of such records should be designed to avoid transcription errors. The record should carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained.

Before any packaging operation begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.

The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

a) the name of the product;
b) the date(s) and times of the packaging operations;
c) the name of the responsible person carrying out the packaging operation;
d) the initials of the operators of the different significant steps;
e) records of checks for identity and conformity with the packaging instructions including the results of in-process controls;
f) details of the packaging operations carried out, including references to equipment and the packaging lines used;
g) whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
h) notes on any special problems or unusual events including details with signed authorisation for any deviation from the manufacturing formula and processing instructions;
i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

Procedures and records

Receipt

4.19 There should be written procedures and records for the receipt of each delivery of each starting, primary and printed packaging material.

4.20 The records of the receipts should include:

a) the name of the material on the delivery note and the containers;
b) the 'in-house' name and/or code of material if different from a);
c) date of receipt;
d) supplier's name and, if possible, manufacturer's name;
e) manufacturer's batch or reference number;
f) total quantity, and number of containers received;
g) the batch number assigned after receipt;
h) any relevant comment (e.g. state of the containers).

4.21 There should be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

Sampling

4.22 There should be written procedures for sampling, which include the person(s) authorised to take samples, the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality (see Section 6, Item 13).

Testing

4.23 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded (see Section 6, Item 17).

Other

4.24 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by the authorised person(s) designated for the purpose.

4.25 Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary (see Section 8).

4.26 There should be written procedures and the associated records of actions taken or conclusions reached, where appropriate, for:

- validation;
- equipment assembly and calibration;
- maintenance, cleaning and sanitisation;
- personnel matters including training, clothing, hygiene;
- environmental monitoring;
- pest control;
- complaints;
- recalls;
- returns.

4.27 Clear operating procedures should be available for major items of manufacturing and test equipment.

4.28 Log books should be kept for major or critical equipment recording, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried out these operations.

4.29 Log books should also record in chronological order the use of major or critical equipment and the areas where the products have been processed.

5 PRODUCTION

Principle

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorisations.

General

5.1 Production should be performed and supervised by competent people.

5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.

5.4 Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.

5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

5.6 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

5.7 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

5.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

5.9 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

5.10 At every stage of processing, products and materials should be protected from microbial and other contamination.

5.11 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitising materials.

5.12 At all times during processing, all materials, bulk containers, major items of equipment and, where appropriate, rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

5.13 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (e.g. quarantined, accepted, rejected, clean).

5.14 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportafion of products from one area to another are connected in a correct manner.

5.15 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.

5.16 Access to production premises should be restricted to authorised personnel.

5.17 Normally, the production of non-veterinary medicinal products should be avoided in areas and with the equipment destined for the production of veterinary medicinal products.

Prevention of cross-contamination in production

5.18 Contaminaflon of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitising materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

5.19 Cross-contamination should be avoided by appropriate technical or organisational measures, for example:

a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;
b) providing appropriate air-locks and air extraction;
c) minimising the risk of contamination caused by re-circulation or re-entry of untreated or insufficiently treated air;
d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed;
e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
f) using 'closed systems' of production;
g) testing for residues and use of cleaning status labels on equipment.

5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

Validation

5.21 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

5.22 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.23 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.

5.24 Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

Starting materials

5.25 The purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers.

5.26 Starting materials should be purchased only from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements, as well as complaints and rejection procedures, are discussed with the manufacturer and the supplier.

5.27 For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.

5.28 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

5.29 Starting materials in the storage area should be appropriately labelled (see Section 5, Item 13). Labels should bear at least the following information:

- the designated name of the product and the internal code reference where applicable;
- a batch number given at receipt;
- where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
- where appropriate, an expiry date or a date beyond which re-testing is necessary.

When fully computerised storage systems are used, all the above information should not necessarily be in a legible form on the label.

5.30 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Section 6, Item 13).

5.31 Only starting materials that have been released by the Quality Control Department and that are within their shelf-life should be used.

5.32 Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

5.33 Each dispensed material and its weight or volume should be independently checked and the check recorded.

5.34 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

Processing operations: intermediate and bulk products

5.35 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.

5.36 Intermediate and bulk products should be kept under appropriate conditions.

5.37 Critical processes should be validated (see 'Validation' in this Section).

5.38 Any necessary in-process controls and environmental controls should be carried out and recorded.

5.39 Any significant deviation from the expected yield should be recorded and investigated.

Packaging materials

5.40 The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

5.41 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorised access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorised personnel following an approved and documented procedure.

5.42 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

5.43 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

Packaging operations

5.44 When setting up a programme for the packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

5.45 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate checklist.

5.46 The name and batch number of the product being handled should be displayed at each packaging station or line.

5.47 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

5.48 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

5.49 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

5.50 The correct performance of any printing operation (e.g. code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.

5.51 Special care should be taken when using cut-labels and when overprinting is carried out offline. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

5.52 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

5.53 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.54 On-line control of the product during packaging should include at least checking the following:

a) general appearance of the packages;
b) whether the packages are complete;
c) whether the correct products and packaging materials are used;
d) whether any over-printing is correct;
e) correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

5.55 Products that have been involved in an unusual event should be reintroduced into the process only after special inspection, investigation and approval by authorised personnel. Detailed records should be kept of this operation.

5.56 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

5.57 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

Finished products

5.58 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

5.59 The evaluation of finished products and documentation that is necessary before release of product for sale are described in Section 6 (Quality Control).

5.60 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

Rejected, recovered and returned materials

5.61 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorised personnel.

5.62 The reprocessing of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Records should be kept of the reprocessing.

5.63 The recovery of all or part of earlier batches that conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorised beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be recorded.

5.64 The need for additional testing of any finished product that has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.65 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for resale, relabelling or recovery with a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse, although basic chemical re-processing to recover active ingredients may be possible. Any action taken should be appropriately recorded.

6 QUALITY CONTROL

Principle

Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to the laboratory operations, but must be involved in all decisions that may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.

General

6.1 Each holder of a manufacturing authorisation should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at their disposal. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out.

6.2 The principal duties of the head of Quality Control are summarised in Section 2. The Quality Control Department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, keep the reference samples of materials and products, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with finished product specification, and examination of the final finished pack.

6.4 Quality control personnel should have access to production areas for sampling and investigation as appropriate.

Good Quality Control Laboratory Practice

6.5 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Section 3.

6.6 The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in Section 7 (Contract Analysis), can be accepted for particular reasons, but this should be stated in the Quality Control records.

Documentation

6.7 Laboratory documentation should follow the principles given in Section 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:

- specifications;
- sampling procedures;
- testing procedures and records (including analytical worksheets and/or laboratory notebooks);
- analytical reports and/or certificates;
- data from environmental monitoring, where required; validation records of test methods, where applicable; procedures for and records of the calibration of instruments and maintenance of equipment.

6.8 Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch and at least five years after the date of manufacture for products with no expiry date.

6.9 For some kinds of data (e.g. analytical tests results, yields, environmental controls) it is recommended that records be kept in a manner permitting trend evaluation.

6.10 In addition to the information that is part of the batch record, other original data such as laboratory notebooks and/or records should be retained and be readily available.

Sampling

6.11 The sample taking should be done in accordance with approved written procedures that describe:

- the method of sampling;
- the equipment to be used;
- the amount of the sample to be taken;
- instructions for any required subdivision of the sample;
- the type and condition of the sample container to be used;
- the identification of containers sampled;
- any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
- the storage conditions;
- instructions for the cleaning and storage of sampling equipment.

6.12 Reference samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process).

6.13 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.

6.14 Reference samples from each batch of finished products should be retained till one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) should be retained for at least two years after the release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. Reference samples of materials and products should be of a size sufficient to permit at least a full re-examination.

Testing

6.15 Analytical methods should be validated. All testing operations described in the marketing authorisation should be carried out according to the approved methods.

6.16 The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be critically examined.

6.17 The tests performed should be recorded and the records should include at least the following data:

a) name of the material or product and, where applicable, dosage form;
b) batch number and, where appropriate, the manufacturer and/or supplier;
c) references to the relevant specifications and testing procedures;
d) test results, including observations and calculations, and reference to any certificates of analysis;
e) dates of testing;
f) initials of the persons who performed the testing;
g) initials of the persons who verified the testing and the calculations, where appropriate;
h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

6.18 All the in-process controls, including those made in the Production area by Production personnel, should be performed according to methods approved by Quality Control and the results recorded.

6.19 Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They should be prepared in accordance with written procedures.

6.20 Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last current factor should be indicated.

6.21 Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

6.22 Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

7 CONTRACT MANUFACTURE AND ANALYSIS

Principle

Contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product or work of unsatisfactory quality. There must be a written contract between the contract giver and the contract acceptor that clearly establishes the duties of each party. The contract must clearly state the way in which the authorised person releasing each batch of product for sale exercises his/her responsibility.

General

7.1 There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

7.2 All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements, should be in accordance with the marketing authorisation for the product concerned.

The contract giver

7.3 The contract giver is responsible for assessing the competence of the contract acceptor to carry out successfully the work required and for ensuring by means of the contract that the principles and guidelines of GMP as interpreted in this guide are followed.

7.4 The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorisation and any other legal requirements. The contract giver should ensure that the contract acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to their premises, equipment, personnel, other materials or other products.

7.5 The contract giver should ensure that all processed products and materials delivered to them by the contract acceptor comply with their specifications or that the products have been released by an authorised person.

The contract acceptor

7.6 The contract acceptor must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the contract giver. Contract manufacture may be undertaken only by an approved manufacturer.

7.7 The contract acceptor should ensure that all products or materials delivered to them are suitable for their intended purpose.

7.8 The contract acceptor should not pass to a third party any of the work entrusted to them under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract acceptor.

7.9 The contract acceptor should refrain from any activity that may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

The contract

7.10 A contract should be drawn up between the contract giver and the contract acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and Good Manufacturing Practice. All arrangements for manufacture and analysis must be in accordance with the manufacturing authorisation and agreed by both parties.

7.11 The contract should specify the way in which the authorised person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of manufacturing authorisation.

7.12 The contract should describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract acceptor should take samples at the premises of the manufacturer.

7.13 Manufacturing, analytical and distribution records, and reference samples should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the contract giver.

7.14 The contract should permit the contract giver to visit the facilities of the contract acceptor.

7.15 In case of contract analysis, the contract acceptor should understand that they are subject to inspection by the competent authorities.

8 COMPLAINTS AND PRODUCT RECALL

Principle

All complaints and other information concerning potentially defective products must be reviewed carefully according to written procedures. In order to provide for all contingencies, a system should be designed to recall promptly and effectively, if necessary, products known or suspected to be defective from the market.

Complaints

8.1 A person should be designated responsible for handling the complaints and deciding the measures to be taken, together with sufficient supporting staff to assist. If this person is not the authorised person, the latter should be made aware of any complaint, investigation or recall.

8.2 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

8.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control should normally be involved in the study of such problems.

8.4 If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected. In particular, other batches that may contain reworks of the defective batch should be investigated.

8.5 All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

8.6 Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

8.7 The regulatory authority should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, or any other serious quality problems with a product.

Recalls

8.8 A person should be designated as responsible for execution and coordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organisation. If this person is not the authorised person, the latter should be made aware of any recall operation.

8.9 There should be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.

8.10 Recall operations should be capable of being initiated promptly and at any time.

8.11 All regulatory authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of being, defective.

8.12 The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.

8.13 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.

8.14 The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.

8.15 The effectiveness of the arrangements for recalls should be evaluated from time to time.

9 SELF INSPECTION

Principle

Self inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.

9.1 Personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a prearranged programme in order to verify their conformity with the principles of Quality Assurance.

9.2 Self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits by external experts may also be useful.

9.3 All self inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.

ANNEXES

A complete list of the annexes pertaining to medicinal products in the European Union is available at the following website: http://pharmacos.eudra.org/F2/eudralex/vol-4/home.htm

Only annexes relevant to the manufacture of veterinary medicinal products in New Zealand are included in this document.

ANNEX 1:
MANUFACTURE OF STERILE (VETERINARY) MEDICINAL PRODUCTS

ANNEX 4:
MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

ANNEX 5:
MANUFACTURE OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

ANNEX 8:
SAMPLING OF STARTING AND PACKAGING MATERIALS

ANNEX 9:
MANUFACTURE OF LIQUIDS, CREAMS AND OINTMENTS

ANNEX 11:
COMPUTERISED SYSTEMS

ANNEX 1:
MANUFACTURE OF STERILE VETERINARY MEDICINAL PRODUCTS

Principle

The manufacture of sterile products is subject to special requirements in order to minimise risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

General

1 The manufacture of sterile products should be carried out in clean areas, entry to which should be through air-locks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air that has passed through filters of an appropriate efficiency.

2 The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area.

Manufacturing operations are divided into two categories: firstly those where the product is terminally sterilised, and secondly those that are conducted aseptically at some or all stages.

3 Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risks of particulate or microbial contamination of the product or materials being handled.

In order to meet 'in operation' conditions these areas should be designed to reach certain specified air cleanliness levels in the 'at rest'occupancy state. The 'at rest' state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The 'in operation' state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

For the manufacture of sterile medicinal products there are normally 4 grades of clean areas.

Grade A:
The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed of 0.45 m/s ± 20% (guidance value) at the working position.

Grade B:
For aseptic preparation and filling, this is the background environment for Grade A zone.

Grades C and D:
Clean areas for carrying out less critical stages in the manufacture of sterile products.

The airborne particulate classification for these grades is given in the following table.

	at rest (b)		in operation	
Grade	maximum permitted number of particles/m^3 equal to or above			
	0.5 µm	5 µm	0.5 µm	5µm
A	3500	0	3500	0
B (a)	3500	0	350000	2000
C (a)	350000	2000	3500000	20000
D (a)	3500000	20000	not defined(c)	not defined(c)

Notes

(a) In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate filters such as HEPA for Grades A, B and C.

(b) The guidance given for the maximum permitted number of particles in the 'at rest' condition corresponds approximately to the US Federal Standard 209 E and the ISO classifications as follows: Grades A and B correspond with class 100, M 3.5, ISO 5; Grade C with class 10.000, M 5.5, ISO 7; and Grade D with class 100.000, M 6.5, ISO 8.

(c) The requirement and limit for this area will depend on the nature of the operations carried out.

Examples of operations to be carried out in the various grades are given in the table below (see also par. 11 and 12)

Grade	Examples of operations for terminally sterilised products (see par. 11)
A	Filling of products, when unusually at risk.
C	Preparation of solutions, when unusually at risk. Filling of products.
D	Preparation of solutions and components for subsequent filling.

Grade	Examples of operations for aseptic preparations (see par. 12)
A	Aseptic preparation and filling.
C	Preparation of solutions to be filtered.
D	Handling of components after washing.

The particulate conditions given in the table for the 'at rest' state should be achieved in the unmanned state after a short 'clean up' period of 15-20 minutes (guidance value), after completion of operations. The particulate conditions for Grade A in operation given in the table should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

4 The areas should be monitored during operation, in order to control the particulate cleanliness of the various grades.

5 Where aseptic operations are performed, monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations.

Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitisation.

Recommended limits for microbiological monitoring of clean areas during operation

Recommended limits for microbial contamination (a)				
Grade	air sample cfu/m^3	settle plates (diam. 9 0 mm), cfu/4 hours (b)	contact plates (diam. 55 mm), cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes

(a) These are average values.

(b) Individual settle plates may be exposed for less than 4 hours.

6 Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, operating procedures should prescribe corrective action.

Isolator technology

7 The utilisation of isolator technology to minimise human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for the respective zones can be realised. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from a single door to double door designs to fully sealed systems incorporating sterilisation mechanisms.

The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high risk manipulations, although it is recognised that laminar air flow may not exist in the working zone of all such devices. The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing it should be at least Grade D.

8 Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitisation of the isolator, the transfer process and isolator integrity.

9 Monitoring should be carried out routinely and should include frequent leak testing of the isolator and glove/sleeve system.

Blow/fill/seal technology

10 Blow/fill/seal units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective Grade A air shower may be installed in at least a Grade C environment, provided that Grade A/ B clothing is used. The environment should comply with the viable and non-viable limits at rest, and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products that are terminally sterilised should be installed in at least a Grade D environment.

Because of this special technology particular attention should be paid to at least the following: equipment design and qualification, validation and reproducibility of cleaning-in-place and sterlisation-in-place, background cleanroom environment in which the equipment is located, operator training and clothing, and interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

Terminally sterilised products

11 Preparation of components and most products should be done in at least a Grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilisation. Where the product is at a high or unusual risk of microbial contamination (for example because the product actively supports microbial growth or must be held for a long period before sterilisation or is necessarily processed not mainly in closed vessels), then preparation should be carried out in a Grade C environment.

Filling of products for terminal sterilisation should be carried out in at least a Grade C environment. The same conditions are recommended for small volume parenterals.

Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a Grade A zone with at least a Grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be carried out in a Grade C environment before terminal sterilisation.

Aseptic preparations

12 Components after washing should be handled in at least a Grade D environment. Handling of sterile starting materials and components, unless subjected to sterilisation or filtration through a micro-organism retaining filter later in the process, should be done in a Grade A environment with a Grade B background.

Preparation of solutions that are to be sterile filtered during the process should be done in a Grade C environment; if not filtered, the preparation of materials and products should be done in a Grade A environment with a Grade B background.

Handling and filling of aseptically prepared products should be done in a Grade A environment with a Grade B background.

Prior to the completion of stoppering, transfer of partially closed containers, as used in freeze drying, should be done either in a Grade A environment with a Grade B background or in sealed transfer trays in a Grade B environment.

Preparation and filling of ointments, creams, suspensions and emulsions should be done in a Grade A environment with a Grade B background, when the product is exposed and is not subsequently filtered.

Personnel

13 Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. Inspections and controls should be conducted from outside the clean areas as far as possible.

14 All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products, including reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care should be taken over their instruction and supervision.

15 Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms, other than those used in the current manufacturing process, should not enter sterile product areas unless rigorous and clearly defined decontamination procedures have been followed.

16 High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard should be decided by a designated competent person.

17 Changing and washing should follow a written procedure designed to minimise contamination of clean area clothing or carry-through of contaminants to the clean area.

18 Wristwatches, makeup and jewellery should not be worn in clean areas.

19 The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination.

The description of clothing required for each grade is given below:

Grade D:
Hair and, where appropriate, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.

Grade C:
Hair and, where relevant, beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.

Grades A/B:
Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.

20 Outdoor clothing should not be brought into changing rooms leading to Grade B and C rooms. For every worker in a Grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session, or at least once a day if monitoring results justify this. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least at every working session.

21 Clean area clothing should be cleaned and handled in such a way that it does not gather additional particulate contaminants that can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.

Premises

22 In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimise the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.

23 To reduce accumulation of dust and to facilitate cleaning there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors are undesirable for this reason.

24 False ceilings should be sealed to prevent contamination from the space above them.

25 Pipes, ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean.

26 Sinks and drains should be prohibited in Grade A/B areas used for aseptic manufacture. In other areas, air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent backflow.

27 Changing rooms should be designed as air-locks and used to provide separation of the different stages of changing and so minimise microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general, hand washing facilities should be provided only in the first stage of the changing rooms.

28 Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.

29 A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10-15 pascals (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components that contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination facilities and treatment of air leaving a clean area may be necessary for some operations.

30 It should be demonstrated that air flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle-generating person, operation, or machine to a zone of higher product risk.

31 A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.

Equipment

32 A conveyor belt should not pass through a partition between a Grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilised (e.g. in a sterilising tunnel).

33 As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilisation is required, it should be carried out, wherever possible, after complete reassembly.

34 When equipment maintenance has been carried out within the clean area, the area should be cleaned, disinfected and/or sterilised where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.

35 Water treatment plants and distribution system should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injections should be produced, stored and distributed in a manner that prevents microbial growth, e.g. by constant circulation at temperatures above 70^0C.

36 All equipment such as sterilisers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their return to use should be approved.

Sanitation

37 The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written programme.Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development of resistant strains.

38 Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.

39 Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

Processing

40 Precautions to minimise contamination should be taken during all processing stages including the stages before sterilisation.

41 Preparations of microbiological origin should not be made or filled in areas used for the processing of other medicinal products; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.

42 Validation of aseptic processing should include simulating the process using a nutrient medium. The form of the nutrient medium used should generally be equivalent to the dosage form of the product. The process simulation test should imitate, as closely as possible, the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. Process simulation should be repeated at defined intervals and after any significant modification to the equipment and process. The number of containers used for a medium fill should be sufficient to enable a valid evaluation. For small batches, the number of containers for the medium fill should at least equal the size of the product batch. The contamination rate should be less than 0.1% with 95% confidence level.

43 Care should be taken that any validation does not compromise the process.

44 Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records should be maintained of the results of the monitoring and of any action taken.

45 Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum, and movement of personnel should be controlled and methodical to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.

46 Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.

47 Containers and materials liable to generate fibres should be minimised in clean areas.

48 Where appropriate, measures should be taken to minimise the particulate contamination of the end product.

49 Components, containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated.

50 The interval between the washing and drying and the sterilisation of components, containers and equipment as well as between their sterilisation and use should be minimised and subject to a time limit appropriate to the storage conditions.

51 The time between the start of the preparation of a solution and its sterilisation or filtration through a micro-organism retaining filter should be minimised. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.

52 The bioburden should be monitored before sterilisation. There should be working limits on contamination immediately before sterilisation which are related to the efficiency of the method to be used. Where appropriate the absence of pyrogens should be monitored. All solutions, in particular large volume infusion fluids, should be passed through a micro-organism retaining filter, if possible sited immediately before filling.

53 Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilised and passed into the area through double-ended sterilisers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Non-combustible gases should be passed through micro-organism retentive filters.

54 The efficacy of any new procedure should be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.

Sterilisation

55 All sterilisation processes should be validated. Particular attention should be given when the adopted sterilisation method is not described in the current edition of the European or other relevant Pharmacopoeia, or when it is used for a preparation which is not a simple aqueous or oily solution. Where possible, heat sterilisation is the method of choice. In any case, the sterilisation process must be in accordance with the marketing and manufacturing authorisations.

56 Before any sterilisation process is adopted its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

57 For effective sterilisation the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.

58 Validated loading patterns should be established for all sterilisation processes.

59 Biological indicators should be considered as an additional method for monitoring the sterilisation. They should be stored and used according to the manufacturer's instructions, and their quality checked by positive controls.

If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.

60 There should be a clear means of differentiating products which have not been sterilised from those which have. Each basket, tray or other carrier of products or components should be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilisation process, but they do not give a reliable indication that the lot is, in fact, sterile.

61 Sterilisation records should be available for each sterilisation run. They should be approved as part of the batch release procedure.

Sterilisation by heat

62 Each heat sterilisation cycle should be recorded on a time/temperature chart with a sufficiently large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation, and where applicable also checked against a second independent temperature probe located at the same position.

63 Chemical or biological indicators may also be used, but should not take the place of physical measurements.

64 Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time period is commenced. This time must be determined for each type of load to be processed.

65 After the high temperature phase of a heat sterilisation cycle, precautions should be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product should be sterilised, unless it can be shown that any leaking container would not be approved for use.

Moist heat

66 Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be routinely checked against the chart recorder during the sterilisation period. For sterilisers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilisation period. There should be frequent leak tests on the chamber when a vacuum phase is part of the cycle.

67 The items to be sterilised, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilisation. All parts of the load should be in contact with the sterilising agent at the required temperature for the required time.

68 Care should be taken to ensure that steam used for sterilisation is of suitable quality and does not contain additives at a level that could cause contamination of product or equipment.

Dry heat

69 The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins may be required as part of the validation.

Sterilisation by radiation

70 Radiation sterilisation is used mainly for the sterilisation of heat sensitive materials and products. Many medicinal products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not normally an acceptable method of sterilisation.

71 During the sterilisation procedure the radiation dose should be measured. For this purpose, dosimetry indicators that are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number, and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used they should be used within the time limit of their calibration. Dosimeter absorbences should be read within a short period after exposure to radiation.

72 Biological indicators may be used as an additional control.

73 Validation procedures should ensure that the effects of variations in density of the packages are considered.

74 Materials handling procedures should prevent mix-up between irradiated and non-irradiated materials. Radiation sensitive colour disks should also be used on each package to differentiate between packages that have been subjected to irradiation and those that have not.

75 The total radiation dose should be administered within a predetermined time span.

Sterilisation with ethylene oxide

76 This method should be used only when no other method is practicable. During process validation it should be shown that there is no damaging effect on the product, and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.

77 Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

78 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimise the time before sterilisation.

79 Each sterilisation cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.

80 For each sterilisation cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration and total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.

81 After sterilisation, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should be validated.

Filtration of medicinal products that cannot be sterilised in their final container

82 Filtration alone is not considered sufficient when sterilisation in the final container is possible. With regard to methods currently available, steam sterilisation is to be preferred. If the product cannot be sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment.

83 Due to the potential additional risks of the filtration method as compared with other sterilisation processes, a second filtration via a further sterilised micro-organism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.

84 Fibre shedding characteristics of filters should be minimal.

85 The integrity of the sterilised filter should be verified before use and should be confirmed by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation, and any significant differences from this during routine manufacturing should be noted and investigated. Results of these checks should be recorded in the batch record. The integrity of critical

gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.

86 The same filter should not be used for more than one working day unless such use has been validated.

87 The filter should not affect the product by removal of ingredients from it or by release of substances into it.

Finishing of sterile products

88 Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules, should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

89 Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, predetermined period.

90 Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eyesight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

Quality control

91 The sterility test applied to the finished product should be regarded only as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.

92 In those cases where parametric release has been authorised, special attention should be paid to the validation and the monitoring of the entire manufacturing process.

93 Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, e.g.:

a) for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention;
b) for products that have been heat sterilised in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

ANNEX 4:
MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Manufacture of premixes for medicated feedingstuffs

For the purposes of these paragraphs:

- **a medicated feedingstuff** is any mixture of a veterinary medicinal product or products and feed or feeds which is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preservative properties or other properties as a medicinal product;

- a **premix for medicated feeding stuffs** is any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feedingstuffs.

1 The manufacture of premixes for medicated feedingstuffs requires the use of large quantities of vegetable matter which is likely to attract insects and rodents. Premises should be designed, equipped and operated to minimise this risk (point 3.4) and should also be subject to a regular pest control programme.

2 Because of the large volume of dust generated during the production of bulk material for premixes, specific attention should be given to the need to avoid cross-contamination and facilitate cleaning (point 3.14), for example through the installation of sealed transport systems and dust extraction, whenever possible. The installation of such systems does not, however, eliminate the need for regular cleaning of production areas.

3 Parts of the process likely to have a significant adverse influence on the stability of active ingredients (e.g. use of steam in pellet manufacture) should be carried out in a uniform manner from batch to batch.

4 Consideration should be given to undertake the manufacture of premixes in dedicated areas which, if at all possible, do not form part of a main manufacturing plant. Alternatively, such dedicated areas should be surrounded by a buffer zone in order to minimise the risk of contamination of other manufacturing areas.

Manufacture of ectoparasiticides

5 In derogation from point 3.6, ectoparasiticides for external application to animals, which are veterinary medicinal products, and subject to marketing authorisation, may be produced and filled on a campaign basis in pesticide specific areas. However, other categories of veterinary medicinal products should not be produced in such areas.

6 Adequate validated cleaning procedures should be employed to prevent cross-contamination, and steps should be taken to ensure the secure storage of the veterinary medicinal product in accordance with the guide.

Manufacture of veterinary medicinal products containing penicillins

7 The use of penicillins in veterinary medicine does not present the same risks of hypersensitivity in animals as in humans. Although incidents of hypersensitivity have been recorded in horses and dogs, there are other materials that are toxic to certain species, e.g. the ionophore antibiotics in horses. Although desirable, the requirements that such products be manufactured in dedicated, self-contained facilities (point 3.6) may be dispensed with in the case of facilities dedicated to the manufacture of veterinary medicinal products only. However, all necessary measures should be taken to avoid cross-contamination and any risk to operator safety in accordance with the guide. In such circumstances, penicillin-containing products should be manufactured on a campaign basis and should be followed by appropriate, validated decontamination and cleaning procedures.

Retention of samples

8 It is recognised that because of the large volume of certain veterinary medicinal products in their final packaging, premixes in particular, it may not be feasible for manufacturers to retain samples from each batch in its final packaging. However, manufacturers should ensure that sufficient representative samples of each batch are retained and stored in accordance with the guide.

9 In all cases, the container used for storage should be composed of the same material as the market primary container in which the product is marketed.

Sterile veterinary medicinal products

10 Where this has been accepted by the competent authorities, terminally sterilised veterinary medicinal products may be manufactured in a clean area of lower grade than the grade required in the annex on ‘Sterile Preparations’, but at least in a Grade D environment.

ANNEX 5:
MANUFACTURE OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Principle

The manufacture of immunological veterinary medicinal products has special characteristics that should be taken into consideration when implementing and assessing the quality assurance system.

Due to the large number of animal species and related pathogenic agents, the variety of products manufactured is very wide and the volume of manufacture is often low; hence work on a campaign basis is common. Moreover, because of the very nature of this manufacture (cultivation steps, lack of terminal sterilisation, etc.), the products must be particularly well-protected against contamination and cross-contamination. The environment also must be protected especially when the manufacture involves the use of pathogenic or exotic biological agents, and the worker must be particularly well protected when the manufacture involves the use of biological agents pathogenic to man.

These factors, together with the inherent variability of immunological products and the relative inefficiency in particular of final product Quality Control tests in providing adequate information about products, means that the role of the Quality Assurance system is of the utmost importance. The need to maintain control over all of the following aspects of GMP, as well as those outlined in this guide, cannot be overemphasised. In particular, it is important that the data generated by the monitoring of the various aspects of GMP (equipment, premises, product etc.) are rigorously assessed, and informed decisions, leading to appropriate action, are made and recorded.

Personnel

1 All personnel (including those concerned with cleaning and maintenance) employed in areas where immunological products are manufactured should be given training in and information on hygiene and microbiology. They should receive additional training specific to the products with which they work.

2 Responsible personnel should be formally trained in some or all of the following fields: bacteriology, biology, biometry, chemistry, immunology, medicine, parasitology, pharmacy, pharmacology, virology and veterinary medicine, and should also have an adequate knowledge of environmental protection measures.

3 Personnel should be protected against possible infection with the biological agents used in manufacture. In the case of biological agents known to cause disease in humans, adequate measures should be taken to prevent infection of personnel working with the agent or with experimental animals.

Where relevant, the personnel should be vaccinated and subject to medical examination.

4 Adequate measures should be taken to prevent biological agents being taken outside the manufacturing plant by personnel acting as a carrier. Dependent on the type of biological agent, such measures may include complete change of clothes and compulsory showering before leaving the production area.

5 For immunological products, the risk of contamination or cross-contamination by personnel is particularly important.

Prevention of contamination by personnel should be achieved by a set of measures and procedures to ensure that appropriate protective clothing is issued during the different stages of the production process.

Prevention of cross-contamination by personnel involved in production should be achieved by a set of measures and procedures to ensure that they do not pass from one area to another unless they have taken appropriate measures to eliminate the risk of contamination. In the course of a working day, personnel should not pass from areas where contamination with live micro-organisms is likely or where animals are housed to premises where other products or organisms are handled. If such passage is unavoidable, clearly defined decontamination procedures, including change of clothing and shoes and, where necessary, showering, should be followed by staff involved in any such production.

Personnel entering a contained area where organisms had not been handled in open circuit operations in the previous twelve hours to check on cultures in sealed, surface decontaminated flasks would not be regarded as being at risk of contamination, unless the organism involved was an exotic.

Premises

6 Premises should be designed in such a way as to control both the risk to the product and to the environment. This can be achieved by the use of contaminant, clean, clean/contained or controlled areas.

7 Live biological agents should be handled in contained areas. The level of containment should depend on the pathogenicity of the micro-organism and whether it has been classified as exotic. (Other relevant legislation also may apply.)

8 Inactivated biological agents should be handled in clean areas. Clean areas should also be used when handling non-infected cells isolated from multicellular organisms and, in some cases, filtration-sterilised media.

9 Open circuit operations involving products or components not subsequently sterilised should be carried out within a laminar air flow work station (Grade A) in a Grade B area.

10 Other operations where live biological agents are handled (quality control, research and diagnostic services etc.) should be appropriately contained and separated if production operations are carried out in the same building. The level of containment should depend on the pathogenicity of the biological agent and whether they have been classified as exotic. Whenever diagnostic activities are carried out, there is the risk of introducing highly pathogenic organisms. Therefore, the level of containment should be adequate to cope with all such risks. Containment may also be required if quality control or other activities are carried out in buildings in close proximity to those used for production.

11 Containment premises should be easily disinfected and should have the following characteristics:

a) the absence of direct venting to the outside;
b) ventilation with air at negative pressure. Air should be extracted through HEPA filters and not be recirculated except to the same area, and provided further HEPA filtration is used (normally this condition would be met by routing the recirculated air through the normal supply HEPAs for that area). However, recycling of air between areas may be permissible provided that it passes through two exhaust HEPAS, the first of which is continuously monitored for integrity, and there are adequate measures for safe venting of exhaust air should this filter fail;
c) air from manufacturing areas used for the handling of exotic organisms should be vented through two sets of HEPA filters in series, and that from production areas not recirculated;
d) a system for the collection and disinfection of liquid effluents including contaminated condensate from sterilisers, biogenerators etc. Solid wastes, including animal carcasses, should be disinfected, sterilised or incinerated as appropriate. Contaminated filters should be removed using a safe method;
e) changing rooms designed and used as air locks, and equipped with washing and showering facilities if appropriate. Air pressure differentials should be such that there is no flow of air between the work area and the external environment or risk of contamination of outer clothing worn outside the area;
f) an air lock system for the passage of equipment, which is constructed so that there is no flow of contaminated air between the work area and the external environment or risk of contamination of equipment within the lock. The air-lock should be of a size which enables the effective surface decontamination of materials being passed through it. Consideration should be given to having a timing device on the door interlock to allow sufficient time for the decontamination process to be effective;
g) in many instances, a barrier double-door autoclave for the secure removal of waste materials and introduction of sterile items.

12 Equipment passes and changing rooms should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time. Changing rooms should be supplied with air filtered to the same standard as that for the work area, and equipped with air extraction facilities to produce an adequate air circulation independent of that of the work area. Equipment passes should normally be ventilated in the same way, but unventilated passes, or those equipped with supply air only, may be acceptable.

13 Production operations such as cell maintenance, media preparation, virus culture, etc. likely to cause contamination should be performed in separate areas. Animals and animal products should be handled with appropriate precautions.

14 Production areas where biological agents particularly resistant to disinfection (e.g. spore-forming bacteria) are handled should be separated and dedicated to that particular purpose until the biological agents have been inactivated.

15 With the exception of blending and subsequent filling operations, one biological agent only should be handled at a time within an area.

16 Production areas should be designed to permit disinfection between campaigns, using validated methods.

17 Production of biological agents may take place in controlled areas provided it is carried out in totally enclosed and heat sterilised equipment, all connections being also heat sterilised after making and before breaking. It may be acceptable for connections to be made under local laminar air flow provided these are few in number and proper aseptic techniques are used, and there is no risk of leakage. The sterilisation parameters used before breaking the connections must be validated for the organisms being used. Different products may be placed in different biogenerators, within the same area, provided that there is no risk of accidental cross-contamination. However, organisms generally subject to special requirements for containment should be in areas dedicated to such products.

18 Animal houses where animals intended or used for production are accommodated should be provided with the appropriate containment and/or clean area measures, and should be separate from other animal accommodation.

Animal houses where animals used for quality control, involving the use of pathogenic biological agents, are accommodated should be adequately contained.

19 Access to manufacturing areas should be restricted to authorised personnel. Clear and concise written procedures should be posted as appropriate.

20 Documentation relating to the premises should be readily available in a plant master file.

The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) so that the designation and conditions of use of all the rooms are correctly identified as well as the biological agents that are handled in them. The flow of people and product should also be clearly marked.

The animal species accommodated in the animal houses or otherwise on the site should be identified.

The activities carried out in the vicinity of the site should also be indicated.

Plans of contained and/or clean area premises should describe the ventilation system indicating inlets and outlets, filters and their specifications, the number of air changes per hour, and pressure gradients. They should indicate which pressure gradients are monitored by pressure indicator.

Equipment

21 The equipment used should be designed and constructed so that it meets the particular requirements for the manufacture of each product.

Before being put into operation the equipment should be qualified and validated and subsequently be regularly maintained and validated.

22 Where appropriate, the equipment should ensure satisfactory primary containment of the biological agents.

Where appropriate, the equipment should be designed and constructed so as to allow easy and effective decontamination and/or sterilisation.

23 Closed equipment used for the primary containment of the biological agents should be designed and constructed so as to prevent any leakage or the formation of droplets and aerosols.

Inlets and outlets for gases should be protected so as to achieve adequate containment e.g. by the use of sterilising hydrophobic filters.

The introduction or removal of material should take place using a sterilisable closed system, or possibly in an appropriate laminar air flow.

24 Equipment where necessary should be properly sterilised before use, preferably by pressurised dry steam. Other methods can be accepted if steam sterilisation cannot be used because of the nature of the equipment. It is important not to overlook such individual items as bench centrifuges and water baths.

Equipment used for purification, separation or concentration should be sterilised or disinfected at least between use for different products. The effect of the sterilisation methods on the effectiveness and validity of the equipment should be studied in order to determine the life span of the equipment.

All sterilisation procedures should be validated.

25 Equipment should be designed so as to prevent any mix-up between different organisms or products. Pipes, valves and filters should be identified as to their function.

Separate incubators should be used for infected and non-infected containers and also generally for different organisms or cells. Incubators containing more than one organism or cell type will be acceptable only if adequate steps are taken to seal, surface decontaminate and segregate the containers. Culture vessels, etc. should be individually labelled. The cleaning and disinfection of the items can be particularly difficult and should receive special attention.

Equipment used for the storage of biological agents or products should be designed and used in such a manner as to prevent any possible mix-up. All stored items should be clearly and unambiguously labelled and in leak-proof containers. Items such as cells and organisms seed stock should be stored in dedicated equipment.

26 Relevant equipment, such as that requiring temperature control, should be fitted with recording and/or alarm systems.

To avoid breakdowns, a system of preventive maintenance, together with trend analysis of recorded data, should be implemented.

27 The loading of freeze driers requires an appropriate clean/contained area.

Unloading freeze driers contaminates the immediate environment. Therefore, for single-ended freeze driers, the clean room should be decontaminated before a further manufacturing batch is introduced into the area, unless this contains the same organisms, and double door freeze driers should be sterilised after each cycle unless opened in a clean area.

Sterilisation of freeze driers should be done in accordance with item 24. In case of campaign working, they should at least be sterilised after each campaign.

Animals and animal houses

28 Quarters for animals used in production and control of biological products should be separated from production and control areas and be suitably designed.

29 The health status of animals from which some starting materials are derived and of those used for quality control and safety testing should be monitored and recorded. Staff employed in such areas must be provided with special clothing and changing facilities.

30 The sanitary status of the animals used for production should be defined, monitored, and recorded. Some animals should be handled as defined in specific monographs (e.g. Specific Pathogens Free Flocks).

31 Animals, biological agents, and tests carried out should be the subject of an identification system so as to prevent any risk of confusion and to control all possible hazards.

Disinfection - Waste disposal

32 Disinfection and/or waste and effluent disposal may be particularly important in the case of manufacture of immunological products. Careful consideration should therefore be given to procedures and equipment, aiming at avoiding environmental contamination as well as to their validation or qualification.

Production

33 Because of the wide variety of products, the frequently large number of stages involved in the manufacture of immunological veterinary medicinal products and the nature of the biological processes, careful attention must be paid to adherence to validated operating procedures, to the constant monitoring of production at all stages and to in-process controls.

Additionally, special consideration should be given to starting materials, media and the use of a seed lot system.

Starting materials

34 The suitability of starting materials should be clearly defined in written specifications. These should include details of the supplier, the method of manufacture, the geographical origin and the animal species from which the materials are derived. The controls to be applied to starting materials must be included. Microbiological controls are particularly important.

35 The results of tests on starting materials must comply with the specifications. Where the tests take a long time (e.g. eggs from SPF flocks) it may be necessary to process starting materials before the results of analytical controls are available. In such cases, the release of a finished product is conditional upon satisfactory results of the tests on starting materials.

36 Special attention should be paid to a knowledge of the supplier's quality assurance system in assessing the suitability of a source and the extent of quality control testing required.

37 Where possible, heat is the preferred method for sterilising starting materials. If necessary, other validated methods, such as irradiation may be used.

Media

38 The ability of media to support the desired growth should be properly validated in advance.

39 Media should preferably be stedrilised in situ or in-line. Heat is the preferred method. Gases, media, acids, alkalis, anti-foaming agents and other materials introduced into sterile biogenerators should themselves be sterile.

40 In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of immunological veterinary medicinal products obtained by microbial, cell or tissue culture, or propagation in embryos and animals, should be based on a system of seed lots or cell banks.

Seed lot and cell bank system

41 The number of generations (doublings, passages) between the seed lot or cell bank and the finished product should be consistent with the dossier of authorisation for marketing.

42 Seed lots and cell banks should be adequately characterised and tested for contaminants. Acceptance criteria for new seed lots should be established. Seed lots and cell banks shall be established, stored and used in such a way as to minimise the risks of contamination, or any alteration. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus or cell lines) shall be handled simultaneously in the same area or by the same person.

43 Establishment of the seed lot and cell bank should be performed in a suitable environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it and the external environment.

44 The origin, form and storage conditions of seed material should be described in full. Evidence of the stability and recovery of the seeds and cells should be provided. Storage containers should be hermetically sealed, clearly labelled and stored at an appropriate temperature. Storage conditions shall be properly monitored. An inventory should be kept and each container accounted for.

45 Only authorised personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Different seed lots or cell banks shall be stored in such a way to avoid confusion or cross-contamination errors. It is desirable to split the seed lots and cell banks and to store the parts at different location so as to minimise the risk of total loss.

Operating principles

46 The formation of droplets and the production of foam should be avoided or minimised during manufacturing processes. Centrifugation and blending procedures, which can lead to droplet formation, should be carried out in appropriate contained or clean/ contained areas to prevent transfer of live organisms.

47 Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Validated decontamination measures should be available for each organism. Where different strains of single bacteria species or very similar viruses are involved, the process need be validated against only one of them, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

48 Operations involving the transfer of materials such as sterile media, cultures or product should be carried out in pre-sterilised closed systems wherever possible. Where this is not possible, transfer operations must be protected by laminar air flow work stations.

49 Addition of media or cultures to biogenerators and other vessels should be carried out under carefully controlled conditions to ensure that contamination is not introduced. Care must be taken to ensure that vessels are correctly connected when addition of cultures takes place.

50 Where necessary, for instance when two or more fermenters are within a single area, sampling and addition ports, and connectors (after connection, before the flow of product, and again before disconnection) should be sterilised with steam. In other circumstances, chemical disinfection of ports and laminar air flow protection of connections may be acceptable.

51 Equipment, glassware, the external surfaces of product containers and other such materials must be disinfected before transfer from a contained area using a validated method (see 47 above). Batch documentation can be a particular problem. Only the absolute minimum required to allow operations to GMP standards should enter and leave the area. If obviously contaminated, such as by spills or aerosols, or if the organism involved is an exotic, the paperwork must be adequately disinfected through an equipment pass, or the information transferred out by such means as photocopy or fax.

52 Liquid or solid wastes such as the debris after harvesting eggs, disposable culture bottles, unwanted cultures or biological agents, are best sterilised or disinfected before transfer from a contained area. However, alternatives such as sealed containers or piping may be appropriate in some cases.

53 Articles and materials, including documentation, entering a production room should be carefully controlled to ensure that only articles and materials concerned with production are introduced. There should be a system which ensures that articles and materials entering a room are reconciled with those leaving so that their accumulation within the room does not occur.

54 Heat stable articles and materials entering a clean area or clean/contained area should do so through a double-ended autoclave or oven. Heat labile articles and materials should enter through an air-lock with interlocked doors where they are disinfected. Sterilisation of articles and materials elsewhere is acceptable provided that they are double wrapped and enter through an air-lock with the appropriate precautions.

55 Precautions must be taken to avoid contamination or confusion during incubation. There should be a cleaning and disinfection procedure for incubators. Containers in incubators should be carefully and clearly labelled.

56 With the exception of blending and subsequent filling operations (or when totally enclosed systems are used) only one live biological agent may be handled within a production room at any given time. Production rooms must be effectively disinfected between the handling of different live biological agents.

57 Products should be inactivated by the addition of inactivant accompanied by sufficient agitation. The mixture should then be transferred to a second sterile vessel, unless the container is of such a size and shape as to be easily inverted and shaken so as to wet all internal surfaces with the final culture/inactivant mixture.

58 Vessels containing inactivated product should not be opened or sampled in areas containing live biological agents. All subsequent processing of inactivated products should take place in clean areas (Grade A-B) or enclosed equipment dedicated to inactivated products.

59 Careful consideration should be given to the validation of methods for sterilisation, disinfection, virus removal and inactivation.

60 Filling should be carried out as soon as possible following production. Containers of bulk product prior to filling should be sealed, appropriately labelled and stored under specified conditions of temperature.

61 There should be a system to assure the integrity and closure of containers after filling.

62 The capping of vials containing live biological agents must be performed in such a way that ensures that contamination of other products or escape of the live agents into other areas or the external environment does not occur.

63 For various reasons there may be a delay between the filling of final containers and their labelling and packaging. Procedures should be specified for the storage of unlabelled containers in order to prevent confusion and to ensure satisfactory storage conditions. Special attention should be paid to the storage of heat labile or photosensitive products. Storage temperatures should be specified.

64 For each stage of production, the yield of product should be reconciled with that expected from that process. Any significant discrepancies should be investigated.

Quality control

65 In-process controls play a specially important role in ensuring the consistency of the quality of biological medicinal products. Those controls which are crucial for the quality (e.g. virus removal) but which cannot be carried out on the finished product, should be performed at an appropriate stage of production.

66 It may be necessary to retain samples of intermediate products in sufficient amount and under appropriate storage conditions to allow repetition or confirmation of a batch control.

67 There may be a requirement for the continuous monitoring of data during a production process, for example monitoring of physical parameters during fermentation.

68 Continuous culture of biological products is a common practice and special consideration needs to be given to the quality control requirements arising from this type of production method.

ANNEX 8:
SAMPLING OF STARTING AND PACKAGING MATERIALS

Principle

Sampling is an important operation in which only a small fraction of a batch is taken. Valid conclusions on the whole cannot be based on tests that have been carried out on nonrepresentative samples. Correct sampling is thus an essential part of a system of Quality Assurance.

Note: Sampling is dealt with in Section 6 of this guide, items 6.11 to 6.14. This annex gives additional guidance on the sampling of starting and packaging materials.

Personnel

1 Personnel who take samples should receive initial and ongoing regular training in the disciplines relevant to correct sampling. This training should include:

- sampling plans;
- written sampling procedures;
- the techniques and equipment for sampling;
- the risks of cross-contamination;
- the precautions to be taken with regard to unstable and/or sterile substances;
- the importance of considering the visual appearance of materials, containers and labels;
- the importance of recording any unexpected or unusual circumstances.

Starting materials

2 The identity of a complete batch of starting materials can normally be ensured only if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly identified on its label.

3 This validation should take account of at least the following aspects:

- nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements of the pharmaceutical industry;
- the Quality Assurance system of the manufacturer of the starting material;
- the manufacturing conditions under which the starting material is produced and controlled;
- the nature of the starting material and the products in which it will be used.

Under such a system, it is possible that a validated procedure exempting identity testing of each incoming container of starting material could be accepted for:

- starting materials coming from a single product manufacturer or plant;
- starting materials coming directly from a manufacturer or in the manufacturer's sealed container where there is a history of reliability, and regular audits of the manufacturer's Quality Assurance system are conducted by the purchaser (the manufacturer of the medicinal product), or by an officially accredited body.

It is improbable that a procedure could be satisfactorily validated for:

- starting materials supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited;
- starting materials for use in parenteral products.

4 The quality of a batch of starting materials may be assessed by taking and testing a representative sample. The samples taken for identity testing could be used for this purpose. The number of samples taken for the preparation of a representative sample should be determined statistically and specified in a sampling plan. The number of individual samples that may be blended to form a composite sample should also be defined, taking into account the nature of the material, knowledge of the supplier and the homogeneity of the composite sample.

Packaging material

5 The sampling plan for packaging materials should take account of at least the following:

- the quantity received;
- the quality required;
- the nature of the material (e.g. primary packaging materials and/or printed packaging materials);
- the production methods; and
- what is known of Quality Assurance system of the packaging matedals'manufacturer based on audits.

The number of samples taken should be determined statistically and specified in a sampling plan.

ANNEX 9:
MANUFACTURE OF LIQUIDS, CREAMS AND OINTMENTS

Principle

Liquids, creams and ointments may be particularly susceptible to microbial and other contamination during manufacture. Therefore special measures must be taken to prevent any contamination.

Premises and equipment

1 The use of closed systems of processing and transfer is recommended in order to protect the product from contamination. Production areas where the products or open clean containers are exposed should normally be effectively ventilated with filtered air.

2 Tanks, containers, pipework and pumps should be designed and installed so that they may be readily cleaned and, if necessary, sanitised. In particular, equipment design should include a minimum of dead-legs or sites where residues can accumulate and promote microbial proliferation.

3 The use of glass apparatus should be avoided wherever possible. High quality stainless steel is often the material of choice for parts coming into contact with product.

Production

4 The chemical and microbiological quality of water used in production should be specified and monitored. Care should be taken in the maintenance of water systems in order to avoid the risk of microbial proliferation. After any chemical sanitisation of the water systems, a validated flushing procedure should be followed to ensure that the sanitising agent has been effectively removed.

5 The quality of materials received in bulk tankers should be checked before they are transferred to bulk storage tanks.

6 Care should be taken when transferring materials via pipelines to ensure that they are delivered to their correct destination.

7 Materials likely to shed fibres or other contaminants, like cardboard or wooden pallets, should not enter the areas where products or clean containers are exposed.

8 Care should be taken to maintain the homogeneity of mixtures, suspensions etc. during filling. Mixing and filling processes should be validated. Special care should be taken at the beginning of a filling process, after stoppages and at the end of the process to ensure that homogeneity is maintained.

9 When the finished product is not immediately packaged, the maximum period of storage and the storage conditions should be specified and adhered to.

ANNEX 11:
COMPUTERISED SYSTEMS

Principle

The introduction of computerised systems into systems of manufacturing, including storage, distribution and quality control does not alter the need to observe the relevant principles given elsewhere in the guide. Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality or quality assurance. Consideration should be given to the risk of losing aspects of the previous system by reducing the involvement of operators.

Personnel

1 It is essential that there is the closest cooperation between key personnel and those involved with computer systems. Persons in responsible positions should have the appropriate training for the management and use of systems within their field of responsibility which utilises computers. This should include ensuring that appropriate expertise is available and used to provide advice on aspects of design, validation, installation and operation of a computerised system.

Validation

2 The extent of validation necessary will depend on a number of factors including the use to which the system is to be put, whether the validation is to be prospective or retrospective and whether or not novel elements are incorporated. Validation should be considered as part of the complete life cycle of a computer system. This cycle includes the stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and changing.

System

3 Attention should be paid to the siting of equipment in suitable conditions where extraneous factors cannot interfere with the system.

4 A written detailed description of the system should be produced (including diagrams as appropriate) and kept up-to-date. It should describe the principles, objectives, security measures and scope of the system and the main features of the way in which the computer is used and how it interacts with other systems and procedures.

5 The software is a critical component of a computerised system. The user of such software should take all reasonable steps to ensure that it has been produced in accordance with a system of quality assurance.

6 The system should include, where appropriate, built-in checks of the correct entry and processing of data.

7 Before a system using a computer is brought into use, it should be thoroughly tested and confirmed as being capable of achieving the desired results. If a manual system is being replaced, the two should be run in parallel for a time, as part of this testing and validation.

8 Data should be entered or amended only by persons authorised to do so. Suitable methods of deterring unauthorised entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals. There should be a defined procedure for the issue, cancellation, and alteration of authorisation to enter and amend data, including the changing of personal passwords. Consideration should be given to systems allowing for recording of attempts to access by unauthorised persons.

9 When critical data are being entered manually (for example the weight and batch number of an ingredient during dispensing), there should be an additional check on the accuracy of the record which is made. This check may be done by a second operator or by validated electronic means.

10 The system should record the identity of operators entering or confirming critical data. Authority to amend entered data should be restricted to nominated persons. Any alteration to an entry of critical data should be authorised and recorded with the reason for the change. Consideration should be given to building into the system the creation of a complete record of all entries and amendments (an 'audit trail').

11 Alterations to a system or to a computer program should be made only in accordance with a defined procedure, which should include provision for validating, checking, approving and implementing the change. Such an alteration should be implemented only with the agreement of the person responsible for the part of the system concerned, and the alteration should be recorded. Every significant modification should be validated.

12 For quality auditing purposes, it should be possible to obtain meaningful printed copies of electronically stored data.

13 Data should be secured by physical or electronic means against wilful or accidental damage, in accordance with item 4.9 of the guide. Stored data should be checked for accessibility, durability and accuracy. If changes are proposed to the computer equipment or its programs, the above mentioned checks should be performed at a frequency appropriate to the storage medium being used.

14 Data should be protected by backing-up at regular intervals. Back-up data should be stored as long as necessary at a separate and secure location.

15 There should be available adequate alternative arrangements for systems that need to be operated in the event of a breakdown. The time required to bring the alternative arrangements into use should be related to the possible urgency of the need to use them. For example, information required to effect a recall must be available at short notice.

16 The procedures to be followed if the system fails or breaks down should be defined and validated. Any failures and remedial action taken should be recorded.

17 A procedure should be established to record and analyse errors and to enable corrective action to be taken.

18 When outside agencies are used to provide a computer service, there should be a formal agreement including a clear statement of the responsibilities of that outside agency (see Section 7).

19 When the release of batches for sale or supply is carried out using a computerised system, the system should allow for only an authorised person to release the batches and it should clearly identify and record the person releasing the batches.

GLOSSARY

Definitions given below apply to the words as used in this guide. They may have different meanings in other contexts.

Air-lock
An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods.

Batch (or Lot)
A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

Note: To complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity.

For control of the finished product, a batch of a proprietary medicinal product comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a given period of time.

Batch number (or lot number)
A distinctive combination of numbers and/or letters that specifically identifies a batch.

Biogenerator
A contained system, such as a fermenter, into which biological agents are introduced along with other materials so as to effect their multiplication or their production of other substances by reaction with the other materials. Biogenerators are generally fitted with devices for regulation, control, connection, material addition and material withdrawal.

Biological agents
Micro-organisms, including genetically engineered micro-organisms, cell cultures and endoparasites, whether pathogenic or not.

Bulk product
Any product that has completed all processing stages up to, but not including, final packaging.

Calibration
The set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

Cell bank
Cell bank system: A cell bank system is a system whereby successive batches of a product are manufactured by culture in cells derived from the same master cell bank. A number of containers from the master cell bank are used to prepare a working cell bank. The cell bank system is validated for a passage level or number of population doublings beyond that achieved during routine production.

Master cell bank: A culture of (fully characterised) cells distributed into containers in a single operation, processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability. A master cell bank is usually stored at -70^0C or lower.

Working cell bank: A culture of cells derived from the master cell bank and intended for use in the preparation of production cell cultures. The working cell bank is usually stored at -70^0C or lower.

Cell culture
The result from the *in vitro* growth of cells isolated from multicellular organisms.

Clean area
An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

Note: The different degrees of environmental control are defined in the Annex for the Manufacture of Sterile Medicinal Products.

Clean/Contained area
An area constructed and operated in such a manner that will achieve the aims of both a clean area and a contained area at the same time.

Containment
The action of confining a biological agent or other entity within a defined space.

Primary containment
A system of containment that prevents the escape of a biological agent into the immediate working environment. It involves the use of closed containers or safety biological cabinets along with secure operating procedures.

Secondary containment
A system of containment prevents the escape of a biological agent into the external environment or into other working areas. It involves the use of rooms with specially designed air handling, the existence of air-locks and/or sterilisers for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment.

Contained area
An area constructed and operated in such a manner (and equipped with appropriate air handling and filtration) so as to prevent contamination of the external environment by biological agents from within the area.

Controlled area
An area constructed and operated in such a manner that some attempt is made to control the introduction of potential contamination (an air supply approximating to Grade D may be appropriate), and the consequences of accidental release of living organisms. The level of control exercised should reflect the nature of the organism employed in the process. At a minimum, the area should be maintained at a pressure negative to the immediate external environment and allow for the efficient removal of small quantities of airborne contaminants.

Computerised system
A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

Cross-contamination
Contamination of a material or of a product with another material or product.

Crude plant (vegetable drug)
Fresh or dried medicinal plant or parts thereof.

Cryogenic vessel
A container designed to contain liquefied gas at extremely low temperature.

Cylinder
A container designed to contain gas at a high pressure.

Exotic organism
A biological agent where either the corresponding disease does not exist in a given country or geographical area, or where the disease is the subject of prophylactic measures or an eradication programme undertaken in the given country or geographical area.

Filling
The dispensing of a bulk product into the final containers for sale as specified in the product registration (marketing authorisation).

Finished product
A medicinal product that has undergone all stages of production, including packaging in its final container.

Herbal medicinal product
Medicinal product containing, as active ingredients, exclusively plant material and/or vegetable drug preparations.

Infected
Contaminated with extraneous biological agents and therefore capable of spreading infection.

In-Process control
Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to specification. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate product
Partly processed material that must undergo further manufacturing steps before it becomes a bulk product.

Liquefiable gases
Those which, at the normal filling temperature and pressure, remain as a liquid in the cylinder.

Manifold
Equipment or apparatus designed to enable one or more gas containers to be filled simultaneously from the same source.

Manufacture
In relation to any agricultural compound, 'manufacture' includes all the following aspects: acquiring materials, making up, preparing, producing or processing, and assessing the agricultural compound for release; it also includes the packing of an agricultural compound in a container for the purposes of sale.

Manufacturer
Any person who manufactures an agricultural compound or veterinary medicine. Where the process of manufacturing an agricultural compound or veterinary medicine is carried out on different sites or by independent contractors on behalf of the registrant, all such contributors shall be recorded as manufacturers of the product and the registrant shall be deemed to be the manufacturer of the product in the register for the purposes of the Act.

Medicinal plant
Plant, the whole or part of which is used for medicinal purpose.

Medicinal product
Any substance or combination of substances presented for treating or preventing disease in animals.

Any substance or combination of substances that may be administered to animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in animals is likewise considered a medicinal product.

Packing
Operations, including filling (in some circumstances), labelling of final containers and their placement in primary (and secondary) packaging to become finished product.

Packaging material
Any material employed in the packing of a medicinal product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Procedures
Description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of a medicinal product.

Production
All operations involved in the preparation of a medicinal product, from receipt of materials through processing and packing, to its completion as a finished product.

Qualification
Action of proving that any equipment works correctly and actually leads to the expected results. The word 'validation' is sometimes widened to incorporate the concept of qualification.

Quality control
See Section 1.

Quarantine
The status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.

Radiopharmaceutical
Any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose.

Reconciliation
A comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used.

Record
See Section 4.

Recovery
The introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

Reprocessing
The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

Return
Sending back to the manufacturer or distributor of a medicinal product which may or may not present a quality defect.

Seed lot
Seed lot system: A seed lot system is a system according to which successive batches of a product are derived from the same master seed lot at a given passage level. For routine production, a working seed lot is prepared from the master seed lot. The final product is derived from the working seed lot and has not undergone more passages from the master seed lot than the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy. The origin and the passage history of the master seed lot and the working seed lot are recorded.

Master seed lot: A culture of a micro-organism distributed from a single bulk into containers in a single operation in such a manner as to ensure uniformity, to prevent contamination and to ensure stability. A master seed lot in liquid form is usually stored at or below -70^0C. A freeze-dried master seed lot is stored at a temperature known to ensure stability.

Working seed lot: A culture of a micro-organism derived from the master seed lot and intended for use in production. Working seed lots are distributed into containers and stored as described above for master seed lots.

Specification
See Section 4.

Starting material
Any substance used in the production of a medicinal product, but excluding packaging materials.

Sterility
Sterility is the absence of living organisms. The conditions of the sterility test are given in the European Pharmacopoeia.

System
Is used in the sense of a regulated pattern of interacting activities and techniques which are united to form an organised whole.

Validation
Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also Qualification).